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(21) International Application Number: PCT/US98/16020 (22) International Filing Date: 31 July 1998 (31.07.98) (30) Priority Data: 08/904,780 1 August 1997 (01.08.97) US 60/067,234 2 December 1997 (02.12.97) US 60/069,547 12 December 1997 (12.12.97) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications US 08/904,780 (CIP) Filed on 1 August 1997 (01.08.97) US 60/067,234 (CIP) Filed on 2 December 1997 (02.12.97) US 60/069,547 (CIP) Filed on 12 December 1997 (12.12.97) (71) Applicant (for all designated States except US): MASSACHUSETTS INSTITUTE OF TECHNOLOGY [US/US]; 77 Massachusetts Avenue, Cambridge, MA 02139 (US).		(72) Inventors; and (75) Inventors/Applicants (for US only): SHASTRI, Venkatram, R. [IN/US]; Apartment #16, 55 Linden Street, Allston, MA 02134 (US). MARTIN, Ivan [US/US]; 52 Dover Street, Somerville, MA 02166 (US). LANGER, Robert, S. [US/US]; 77 Lombard Street, Newton, MA 02158 (US). SEIDEL, Joachim [US/US]; 50 Lexington Avenue, Somerville, MA 02144 (US). (74) Agent: BIEKER-BRADY, Kristina; Clark & Elbing LLP, 176 Federal Street, Boston, MA 02110-2214 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: THREE-DIMENSIONAL POLYMER MATRICES (57) Abstract Matrices that include a macrostructure having a semi-solid network and voids, and a microstructure having voids, in which the microstructure is located within the semi-solid network are disclosed. Methods for preparing these matrices are also disclosed.		

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poly(ether esters).

The particles can be particles of natural waxes, synthetic waxes and wax-like polymers. The waxes and wax-like polymers can be selected from the group consisting of paraffin, beeswax, and low density polyethylene. In other
5 embodiments, the particles are polymer particles. Preferably the size of the particles is between about 50 and 500 μm .

In other preferred embodiments, the polymer/particle mixture includes a component selected from the group consisting of industrial catalysts, diagnostic agents, therapeutic agents. The therapeutic agent can be selected from the
10 group consisting of cells, osteoinductive materials, and osteoconductive materials.

The matrix can be formed into the shape of a hollow tube; formed into a solid object selected from the group consisting of rods, pins, screws, plates and anatomical shapes; formed into a solid object selected from the group
15 consisting of porous electrodes, porous fibers, and porous solid support materials; or formed into particles suitable for pulmonary delivery or injection.

In a twenty-fourth aspect, the invention features a polymer matrix with a porosity between about 10 and 95% which is substantially uniform throughout the matrix, prepared by (a) dissolving a water-soluble polymer in a solution; (b)
20 adding particles with a size of less than 5000 μm to the polymer solution that are insoluble or sparingly soluble in the polymer solvent at the temperature of the polymer solution when the particles are added; (c) mixing the solid particles and the solution to form a polymer/particle mixture; and (d) extracting the particles from the polymer/particle mixture with a solvent that is a solvent for
25 the particles and a non-solvent for the polymer.

"Porous polymer matrix" means any solid object made of a polymer, which forms a continuous or discontinuous porous network. Porous polymer

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matrices include porous membranes, porous foams, and porous beads.

“Macrostructure,” as used herein when referring to a matrix, means the semi-solid network of the matrix and the continuous voids defined by the network.

5 “Microstructure,” as used herein when referring to a matrix, means the system of voids that are contained within the semi-solid network of the matrix.

“Semi-solid,” as used herein when referring to a structure, means that the structure can have voids.

10 “Voids” mean portions of a matrix that do not contain the material that makes up the semi-solid network of the matrix; the voids are filled with any substance that is different from the substance that makes up the majority of the semi-solid network.

The “diameter of a void” means the diameter of the largest sphere that would fit through the opening defined by the void.

15 “Connectivity number” means the number of cuts that must be made in order to ensure that an object is separated into at least two completely separate pieces.

A “cut” means a cut that passes through a meridional circle of the semi-solid network and does not pass through a void of the matrix.

20 A “cross-section” means a section that can be drawn through a portion of the semi-solid network of the matrix by drawing a meridional curve on the exterior surface of the portion.

A “minimum diameter of a cross section” means the shortest straight line that can be drawn that joins two edges of the cross-section and passes
25 through the center of the cross-section.

A “maximum diameter of a cross section” means the longest straight line that can be drawn that joins two edges of the cross-section.

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A "diameter of a cross-section" is the mean of the minimum and maximum diameters.

"Average diameter of the cross sections of the semi-solid network," means the mean of the diameters of the cross sections of the semi-solid
5 network.

"Continuous," as used herein when referring to the semi-solid network, means that the relevant portions of the semi-solid network are joined as one piece. That is, a line can be drawn from one point on the surface to another point without leaving the surface of the semi-solid network and without
10 crossing a void. Similarly, continuous, as used herein when referring to voids, means that a line can be drawn connecting a point in the void space with another point in the void space, without leaving the void space and without crossing the semi-solid network.

"Fractal," as used herein, means an irregular curve or shape that repeats
15 itself over a continuous surface at different scales.

An "exterior face of the matrix" means the face that is adjacent to the mold during formation of the matrix.

"Porogen," as used herein, means a non-gaseous material that is soluble in at least one solvent and sparingly soluble in at least one solvent, that is
20 combined with a material to form a mixture, then removed from the mixture to leave voids.

"Sparingly soluble" describes a material that, under the conditions of processing, has a solubility of less than 30% by weight in the given solvent, and preferably has a solubility of less than 20% by weight, less than 10% by
25 weight, or less than 2% by weight.

"Non-solvent," as used herein, describes a solvent in which a given material is insoluble or sparingly soluble.

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“Hydrophilic” describes a material that has a solubility of at least 0.5% by weight in water.

“Microspheres” describe objects having an average diameter of about 2 μm to about 100 μm . They are composed of synthetic polymers, biological polymers, or blends or combinations thereof.

“Bioactive agent” describes a substance that has a physiological or biological effect on a cell, tissue, organ, or other living structure.

“Biodegradable” means capable of being broken down into innocuous products when placed within a living system, such as a cell culture system, or a living organism, such as a human or animal, or when exposed to bodily fluids.

“Bioerodible” means capable of being dissolved or suspended in biological fluids.

“Bioresorbable” means capable of being absorbed by the cells, tissue, or fluid in a living body.

“Bioerodes at substantially the same rate that cells populate” means that an object, such as a matrix, bioerodes — that is, is dissolved or suspended in biological fluids — at the same rate that cells grow and produce extracellular matrix (ECM), so that the total volume of the matrix material, the cells, and the ECM within the matrix remains substantially constant.

“Substantially constant,” when referring to the total volume of the matrix material, the cells, and the extracellular matrix within the matrix, means a change in the total volume of less than 25%, and preferably less than 15%, or 5%.

“Impermeable,” as used herein, means that cells can migrate into the material to a depth of less than 200 μm .

“Three-dimensional,” as used herein, means that the smallest dimension of an object (e.g., length, width, or depth) is at least 100 μm .

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“Non-friable” means that when cut, the portions separate into masses with a total loss of materials to flaking or powdering being less than 5% of the total mass of the material.

5 The matrices of the invention offer several advantages over existing matrices. The porous nature of the matrices and the high surface areas provide an environment that is permissive to cell ingrowth. In addition, the highly interconnected structure of the matrices provides them with mechanical strength.

10 The methods of the invention provide convenient, cost-effective ways to prepare porous polymer matrices. In addition, the methods of the invention provide novel ways to alter physical properties of the matrices.

Brief Description of the Drawings

15 Fig. 1A is a schematic representation of a mold used to make matrices of the invention; Fig. 1B is a schematic representation of the three permanently connected sides of the mold; Fig. 1C is a schematic representation of four sides of the mold, with one side being connected by means of screws; Fig. 1D is a schematic representation of the top of the mold and the sides of the mold; and Fig. 1E is a schematic representation of the top of the mold.

Fig. 2 is a photograph of a matrix of the invention.

20 Fig. 3A is a schematic representation of a curve; Fig. 3B is a schematic representation of a surface.

Fig. 4A is a schematic representation of the matrix of the invention showing a meridional curve; and Fig. 4B is a schematic representation of a cross section of the matrix, showing the minimum and maximum diameters.

25 Figs. 5A and 5B are photographs of the matrix of the invention.

Fig. 6A is a schematic representation of a curve with a fractal dimension

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Claims

1. A matrix comprising a macrostructure having a semi-solid network and voids, said matrix further comprising a microstructure having voids, wherein said microstructure is located within said semi-solid network.
- 5 2. The matrix of claim 1, wherein said semi-solid network comprises a polymer.
3. The matrix of claim 1, wherein said matrix comprises a copolymer having a carboxylic acid group or a copolymer having an amine group.
4. The matrix of claim 1, wherein said matrix comprises a conductive
10 polymer selected from the group consisting of polypyrrole, polyaniline, polyacetylene, and polythiophene.
5. The matrix of claim 1, wherein said semi-solid network consists essentially of a polymer or mixture of polymers.
6. The matrix of claim 1, wherein the surface area of said matrix is at
15 least 1 m²/g.
7. The matrix of claim 1, wherein the surface area of said matrix is at least 5 m²/g.
8. The matrix of claim 1, wherein the surface area of said matrix is at least 10 m²/g.

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